UDC 547.91.02

100. Ken'ichi Takeda and Hitoshi Minato : Studies on Sesquiterpenoids. I. Absolute Configuration of Guaiol. (1).*1 Absolute Configuration of the Methyl Group at C-4 in Guaiol.

(*Research Laboratory, Shionogi & Co., Ltd.**2)

Some interesting observations were made in the course of the present investigation on the synthesis of linderazulene¹⁾ (X) from guaiol (I) and this fact led to the studies on the elucidation of the stereochemistry of guaiol.

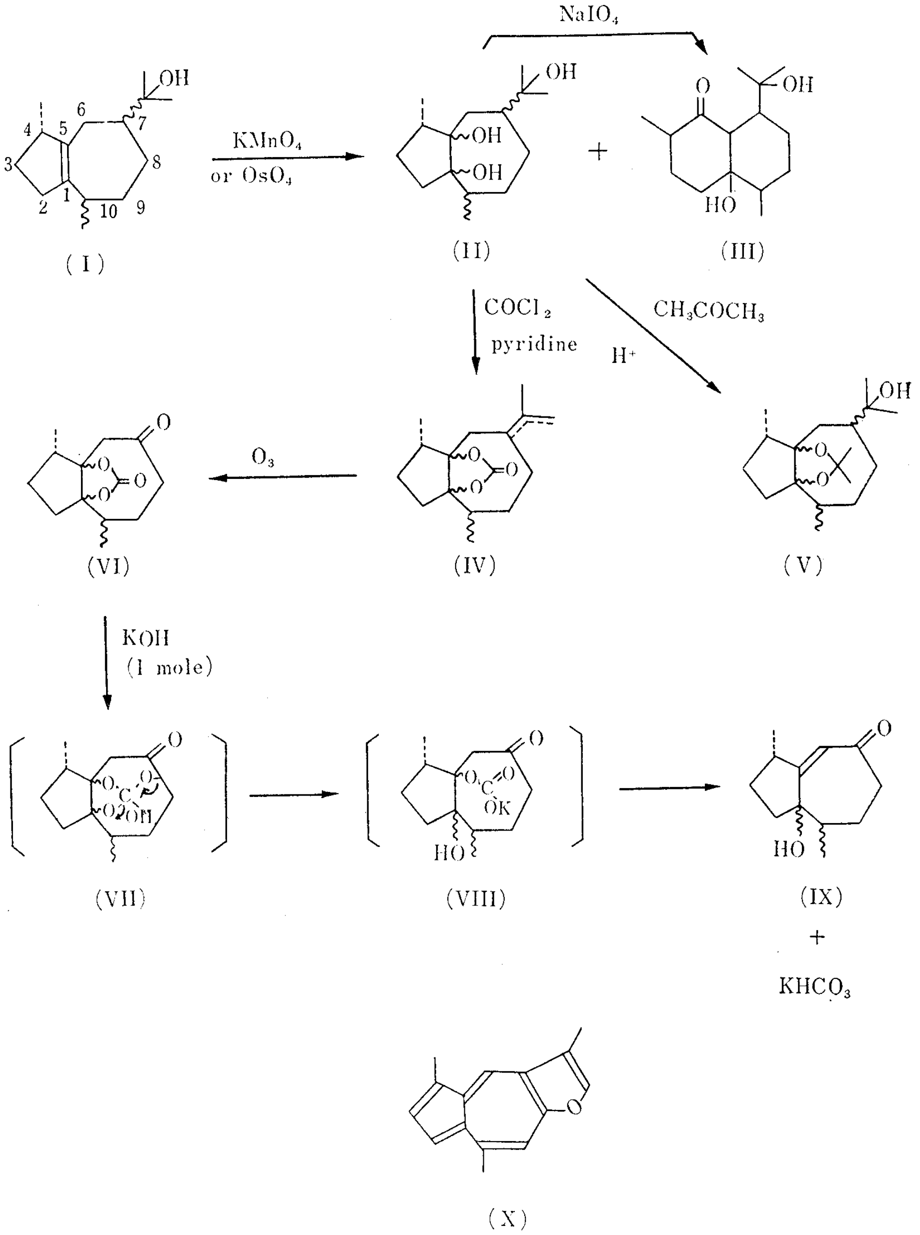

Chart 1.

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*1 A preceding communication : Tetrahedron Letters, No. 22, 33 (1960).

*2 Fukushima-ku, Osaka (武田健一, 湊 均).

1) K. Takeda, W. Nagata : This Bulletin, **1**, 164 (1953).

Informations on the absolute configuration of sesquiterpenes of the perhydroazulene type are largely based on the results of optical rotatory dispersion.[2] The present work was an attempt to decide the absolute configuration of methyl group at C-4 and C-10 in guaiol by degradation of an α,β-unsaturated ketone (IX) (Chart 1), which was obtained during the synthesis of guaiol derivatives and seemed to be a useful substance for this purpose.

When guaiol (I) was oxidized with potassium permanganate, dihydroxyguaiol (II), m.p. 106~107°, and the dihydroxy-ketone[3] (III), m.p. 224~225°, were isolated. The latter was found to be identical with the ozonolysis product of (I) obtained by Ruzicka[4] and also the potassium permanganate oxidation product of (I) obtained by Semmler,[5] but (II) was a new substance, which was also obtained by the action of osmium tetroxide from (I). Since dihydroxyguaiol afforded the known (III) by oxidation with sodium periodate, the structure of this triol was established as (II).

Attempts to obtain acetonide (V) of (II) by means of various catalysts were found to be undesirable (maximum yield, about 30%), but treatment of (II) with phosgene-pyridine easily afforded a carbonate compound. In this case, the hydroxyl group in the side chain was simultaneously dehydrated giving a pale yellow oil (IV), b.p$_{0.09}$ 145°, which consisted of a mixture of isopropenyl and isopropylidene compounds. This carbonate mixture was converted without purification to a ketone (VI), m.p. 113~114°, $[\alpha]_D^{21}$ +2.9°, in ca. 60% yield by ozonolysis.

Although this ketone (VI) was at first prepared as a starting material for synthesis of azulenes, it was now used for the elucidation of absolute configuration. When (VI) was treated with exactly 1 mole of potassium hydroxide at room temperature in ethanol solution, a large amount of colorless crystals of potassium hydrogencarbonate separated from this solution, which filled the flask after 15 minutes. The mixture was allowed to stand at room temperature for 3 hours and filtered off, from which an α,β-unsaturated ketone (IX), m.p. 47~49°, $[\alpha]_D^{20}$ +176.7°, was isolated from the filtrate in excellent yield. In another run, when the reaction mixture was filtered after 15 minutes, potassium

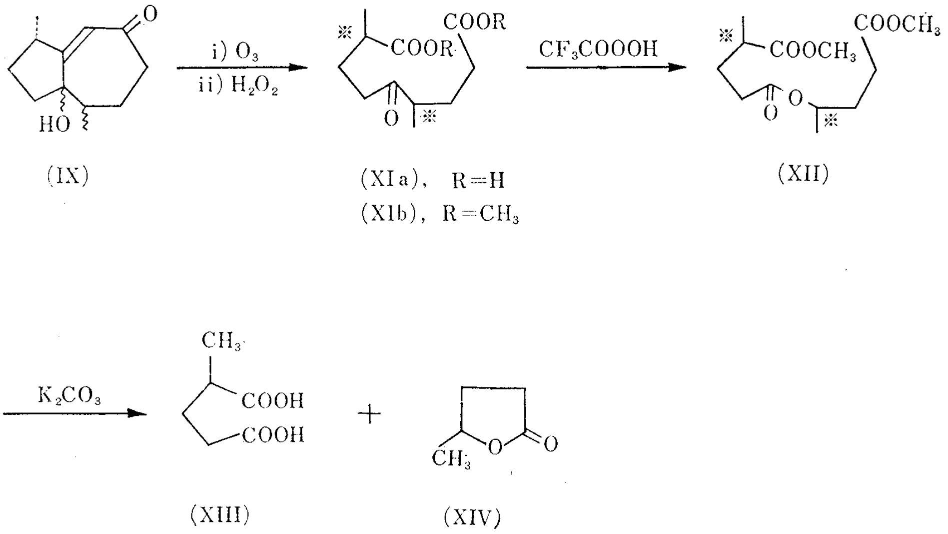

Chart 2.

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2) C. Djerassi, J. Osiecki, W. Herz: J. Org. Chem., **22**, 136 (1957); L. Dolejs, M. Soucek, M. Horak, V. Herout, F. Šorm: Collection Czechoslov. Chem. Communs., **23**, 2195 (1958); D. H. R. Barton, J. E. D. Levisalles: J. Chem. Soc., **1958**, 4518.

3) Pl. A. Plattner, G. Magyer: Helv. Chim. Acta, **24**, 191 (1941).

4) L. Ruzicka, A. J. Haagen-Smit: *Ibid.*, **14**, 1122 (1931).

5) F. W. Semmler, E. W. Mayer: Chem. Ber., **45**, 1391 (1912).

hydrogencarbonate was obtained in ca. 94% yield. This α,β-unsaturated ketone showed an absorption band at 237.5 mμ (ε 9,620) in the ultraviolet region and absorption bands at 3445 (O-H), 1641 (C=O), and 1603 cm^{-1} (C=C) in the infrared region. The results of the spectra support the structure of (IX) and it seemed most likely from these observations that this reaction proceeded with elimination of potassium hydrogencarbonate through the intermediates (VII, VIII), as shown in Chart 1. Hence it was expected that this hydrolysis reaction proceeded in the potassium hydrogencarbonate-alkaline medium, and that the epimerisation at C-4 would not occur in spite of the fact that potassium hydroxide was used in this case.

Ozonolysis of the α,β-unsaturated ketone (IX) in ethyl acetate followed by hydrogen peroxide oxidation in a neutral medium afforded an oily keto-dibasic acid (XIa). Its dimethyl ester (XIb), b.p$_{1.5}$ 134°, $[\alpha]_D^{24}$ +17.1°, obtained by the action of diazomethane, was then rearranged with trifluoroperacetic acid[6] to the ester (XII), b.p$_{2.5}$ 139°, $[\alpha]_D^{21}$ +16.7°, by the Baeyer-Villiger reaction. Since it was shown that the peracid-ketone reaction[7] not only proceeds with retention of configuration of the migrating group, the migrating group being the one with greater capacity for electron release, it was concluded that the C-10 methyl group in the ester (XII) kept its original configuration.

The ester (XII) thus obtained was saponified with potassium carbonate in methanol to yield 2-methylglutaric acid (XIII) as well as 4-hydroxyvaleric γ-lactone (XIV). 2-Methylglutaric acid (XIII), m.p. 85~86°, obtained from this ester showed a positive rotatory power, $[\alpha]_D^{13}$ +17.9°, and it was confirmed that this acid was identical with the synthetic (+)-2-methylglutaric acid, m.p. 82~84°, $[\alpha]_D^{19}$ +15.4°[8] (see Chart 3) by a mixed melting point determination and rotation comparison (see Table I).

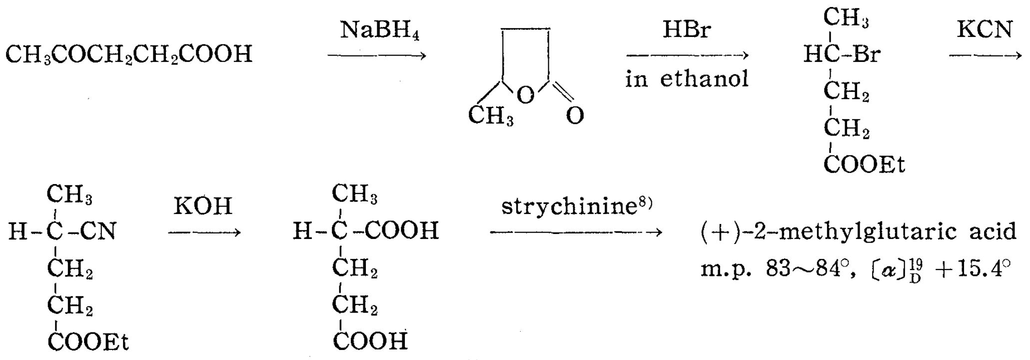

Chart 3.

TABLE I. Comparison of Optical Rotations

	m.p. (°C)	$[\alpha]_D$
(XIII)	85~86	+17.9° (dioxane)
Synthetic (+)-2-methylglutaric acid	83~84	+15.4° (〃)
〃 [a]	81	+20.5° (H_2O)
〃 [b]	81~82	+18.0° ($CHCl_3$)
Synthetic (−)-2-methylglutaric acid[c]	82.5~84.5	−21.2° (〃)

a) E. Berner, R. Leonardson : Ann., **538**, 1 (1939).
b) S.M. McElvain, E.J. Eisenbraun : J. Am. Chem. Soc., **77**, 1599 (1955).
c) E.J. Eisenbraun : *Ibid.*, **77**, 3383 (1955).

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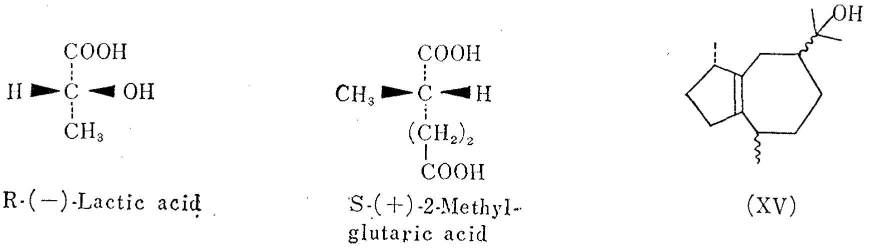
[6] W.D. Emmons, G.B. Lucas : J. Am. Chem. Soc., **77**, 2287 (1955).

[7] R.B. Turner : J. Am. Chem. Soc., **72**, 878 (1950); T.F. Gallagher, T.H. Kritchevsky : *Ibid.*, **72**, 882 (1950); W. von E. Doering, E. Dorfman : *Ibid.*, **75**, 5595 (1953); C.A. Bunton, T.A. Lewis, D. R. Llewellyn : Chem. & Ind. (London), **1954**, 191.

[8] E. Berner, R. Leonardsen : Ann., **538**, 1 (1939).

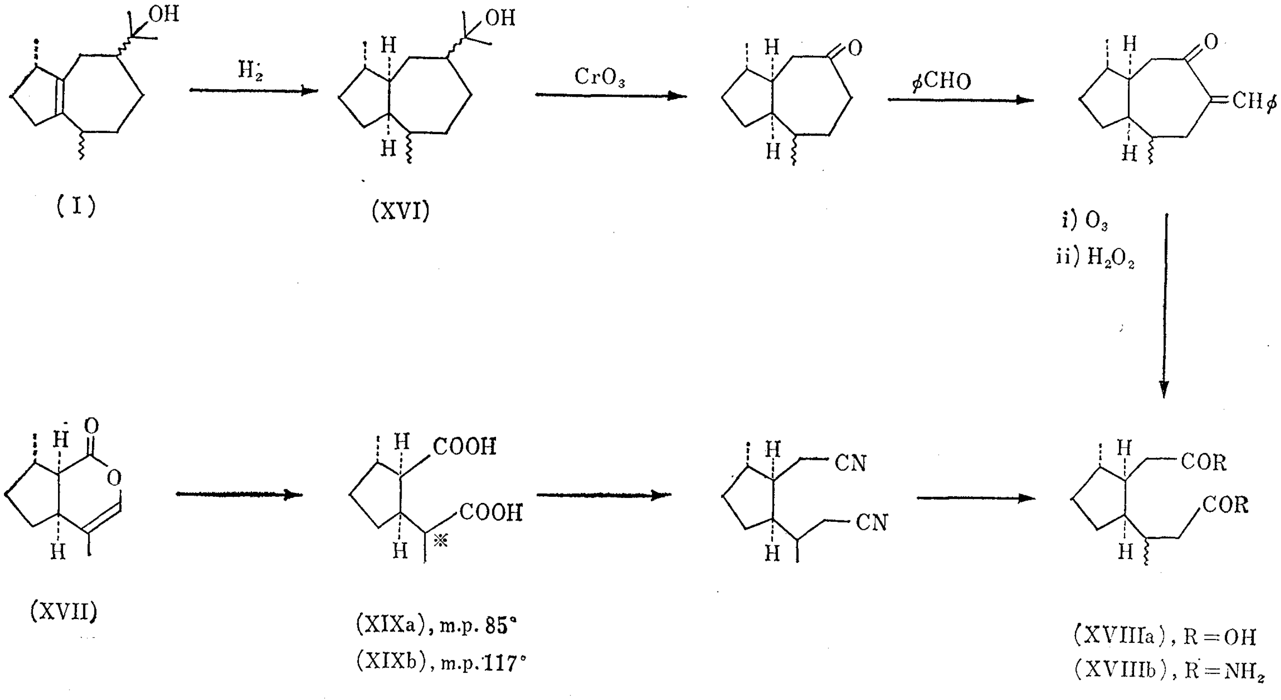
Since S-(+)-2-methylglutaric acid was correlated with R-(−)-lactic acid by Fredga[9] (see Chart 4), (XIII) must belong to S-series. It follows, therefore, that the C-4 methyl group in guaiol possesses the α-configuration[*3], and guaiol should be represented by (XV).



R-(−)-Lactic acid S-(+)-2-Methylglutaric acid (XV)

Chart 4.

Recently, Djerassi's group[10,*4] reported that bis-homonepetalinic acid (XVIIIa) and its acid amide (XVIIIb), obtained from nepetalinic acid (XIXa), m.p. 85~86°, $[\alpha]_D$ +31°, having the known configurations at C-1, C-4, and C-5 in guaiol were identical with the degradation products of *d*-dihydroguaiol (XVI) as shown in Chart 5, and concluded that the C-4 methyl group in guaiol should be α-oriented. These facts are in complete agreement with the present results. The absolute configuration of the methyl group at C-10 in guaiol will be described in the succeeding paper.



(I) (XVI)

(XVII) (XIXa), m.p. 85° (XIXb), m.p. 117° (XVIIIa), R=OH (XVIIIb), R=NH_2

Chart 5.

[*3] The term "α" is used according to the steroidal convention.

[*4] The authors are very much indebted to Dr. Carl Djerassi (Stanford University) for sending them the manuscript of his paper "On the Absolute Configuration of Guaiol. Correlation with Nepetalinic Acid" before publication.

9) A. Fredga: Arkiv. Kemi, Mineral. Geol., **24A**, No. 32 (1947); E.J. Eisenbraun, S.M. McElavin: J. Am. Chem. Soc., **77**, 3383 (1955); A.S. Bailey, V.D. Brice, M.G. Horne, N. Polgar: J. Chem. Soc., **1959**, 661.

10) E.J. Eisenbraun, T. George, B. Riniker, C. Djerassi: J. Am. Chem. Soc., **82**, 3648 (1960).

Experimental[*5]

Oxidation of Guaiol (I)——(a) With Potassium Permanganate : A solution of 4.8 g. (2 equiv.) of $KMnO_4$ in 80 cc. of H_2O was added dropwise to a solution of 3.33 g. of guaiol[11] (I) in 150 cc. of Me_2CO containing 1.5 cc. of 2*N* NaOH, with stirring at 0∼10° for 30 min. After stirring at 5∼10° for an additional 30 min., a solution of 15 g. of $NaHSO_3$ in 50 cc. of H_2O was added to this mixture. After filtration, residual MnO_2 was washed with Me_2CO, the filtrate and washings were combined, and Me_2CO was evaporated *in vacuo*. The residue was extracted with $CHCl_3$, the $CHCl_3$ extract was washed with 2*N* Na_2CO_3 and H_2O, dried over Na_2SO_4, and evaporated, leaving 4 g. of a yellow oil. Fractional crystallization from Me_2CO gave 1.05 g. of (Ⅱ), colorless prisms, m.p. 104∼105°, and 780 mg. of (Ⅲ), colorless plates, m.p. 211∼213°. Dihydroxyguaiol (Ⅱ) was recrystallized from Me_2CO-Et_2O to colorless prisms, m.p. 106∼107°. *Anal.* Calcd. for $C_{15}H_{28}O_3$: C, 70.27; H, 11.01. Found : C, 70.27; H, 10.98. $[\alpha]^{24}_{D}$ $-7°\pm2°$ (c=0.999, dioxane). IR ν^{Nujol}_{max} cm^{-1} : 3385, 1135, 1023, 1010, 897. 815.

(Ⅲ) was recrystallized from MeOH to colorless plates, m.p. 224∼225°. *Anal.* Calcd. for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found : C, 70.84; H, 10.36. IR ν^{Nujol}_{max} cm^{-1} : 3430, 1705, 995.

(b) With Osmium Tetroxide : A solution of 1 g. of OsO_4 in 10 cc. of dehyd. benzene was added to a solution of 870 mg. of guaiol (I) in 15 cc. of dehyd. benzene and 1.5 cc. of pyridine, and allowed to stand for 35 days at room temperature. This mixture was added dropwise to a solution of 7.1 g. of Na_2SO_3 and 7.1 g. of $KHCO_3$ in 68 cc. of H_2O and 46 cc. of MeOH with stirring at room temperature for 30 min. After stirring for an additional 6.5 hr., the dark brown benzene layer faded into yellow. After filtration, the osmium salts were washed with Et_2O. The filtrate and washing were salted out with NaCl, extracted with Et_2O, washed with 2*N* H_2SO_4, 2*N* Na_2CO_3, and H_2O, dried over Na_2SO_4, and Et_2O was evaporated giving 1 g. of a viscous oil. This oil was dissolved in 100 cc. of petr. ether and filtered through a column of 20 g. of Al_2O_3 (Merck) to give 560 mg. of colorless prisms, m.p. 99∼103°. Recrystallization from Et_2O-Me_2CO gave colorless prisms, m.p. 104∼105°, undepressed on admixture with (Ⅱ).

Oxidation of Dihydroxyguaiol (II) with Sodium Periodate——10 cc. (2 equiv.) of 0.1*M* $NaIO_4$ was added to a solution of 128 mg. of (Ⅱ) in 10 cc. of MeOH, and allowed to stand for 74 hr. at room temperature. (The amount of consumption of IO_4^- was determined by iodometry.) This mixture was extracted with $CHCl_3$, washed with 2*N* Na_2CO_3 and H_2O, dried over Na_2SO_4, and evaporated giving 61 mg. of a colorless oil. This oil was dissolved in 6 cc. of petr. ether and chromatographed on 1.5 g. of Al_2O_3 (Merck) to give 46.6 mg. of colorless plates, m.p. 224∼225°, undepressed on admixture with (Ⅲ).

Carbonate (IV) of Dihydroxyguaiol——100 g. of 24% phosgene-dehyd. toluene solution was added dropwise to a solution of 5.12 g. of dihydroxyguaiol (Ⅱ) in 200 cc. of alcohol-free $CHCl_3$ and 65 cc. of pyridine with stirring at −15 to −20° for 40 min. This mixture was stirred for an additional 30 min., allowed to stand at 0° overnight, then poured onto ice-water, and extracted with Et_2O. The extract was washed with 2*N* H_2SO_4, 2*N* Na_2CO_3 and H_2O, dried over Na_2SO_4, and evaporated leaving 5.5 g. of a red brown oil. This oil was chromatographed on 50 g. of neutral Al_2O_3 ("Woelm," Activity Grade Ⅲ) to give 4.02 g. of a yellow viscous oil (Ⅳ), which was distilled to yield a pale yellow viscous oil, b.p$_{0.09}$ 145°, n^{20}_{D} 1.5055, $[\alpha]^{27}_{D}$ $-0.6°\pm2°$ (c=1.720, dioxane). *Anal.* Calcd. for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found : C, 72.69; H, 9.18. IR ν^{film}_{max} cm^{-1} : 1796 (C=O), 1648 (C=C), 1045, 886, 768.

Acetonide (V) of Dihydroxyguaiol——Four drops of conc. HCl was added to a solution of 2.56 g. of dihydroxyguaiol (Ⅱ) in 100 cc. of Me_2CO and the mixture was allowed to stand for 60 hr. at room temperature. The mixture was neutralized with K_2CO_3 solution, evaporated, and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried over Na_2SO_4, and evaporated giving 2.40 g. of a brown oil, which was crystallized on addition of Et_2O to yield 415 mg. of (Ⅱ). The residual oil (1.94 g.) was dissolved in 200 cc. of petr. ether and chromatographed on 60 g. of Al_2O_3 (Merck). From petr. ether-benzene (1:1) and benzene fractions was obtained 560 mg. (19.0% yield) of a pale yellow oil (Ⅴ), b.p$_4$ 154∼155°, ν^{film}_{max} cm^{-1} : 3560 (O-H) and 1020 (C-O). From $CHCl_3$ fraction was recovered 656 mg. of (Ⅱ).

Ozonolysis of (IV)——A solution of 4.07 g. of (Ⅳ) in 40 cc. of AcOEt was treated at −75° with O_3 stream (3.2%, O_3). After 1.5 equiv. of O_3 was absorbed, the solution colored blue, was allowed to stand at −75° for 30 min. The solvent was removed in high vacuum at room temperature to afford a pale yellow viscous oil. To a solution of this residue in 30 cc. of glacial AcOH 10 g. of Zn dust

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[*5] The Rudolph Photoelectric Polarimeter Model 200 was used for all determinations of optical rotations. All melting points were measured by use of Kofler block ("Monoscope" Hans Bock Co., Ltd., Frankfurt am Main, Germany) and corrected.

11) Guaiol was purchased from Polak & Schwarz's Essence-Fabrieken, New York.

was added in small portions with stirring in an ice bath, during which time the temperature was kept below 50°. After the color-test with ZnI_2-starch paper became negative, the mixture was filtered, evaporated *in vacuo*, and extracted with Et_2O. The Et_2O extract was washed with 2*N* Na_2CO_3 and H_2O, dried over Na_2SO_4, and evaporated giving 4.2 g. of a colorless oil, which crystallized on addition of Et_2O. Recrystallization from Et_2O-Me_2CO gave 1.89 g. of (VI), colorless prisms, m.p. 113~114°. *Anal.* Calcd. for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found : C, 65.81; H, 7.70. $[\alpha]_D^{21}$ +2.9° ±2° (c=1.230, dioxane). IR ν_{max}^{Nujol} cm^{-1} : 1784 (C=O), 1716 (C=O), 1049, 1023, 778.
2,4-Dinitrophenylhydrazone : Yellow needles, m.p. 241~243° (from EtOH).

Action of Potassium Hydroxide on (VI)——A solution of 500 mg. of (VI) in 80 cc. of EtOH was added to a solution of 117 mg. (1.0 equiv.) of KOH in 3 drops of H_2O at once, and allowed to stand at room temperature. After a while, the separation of colorless crystals occurred and the flask filled with crystals. This reaction mixture was filtered after 3 hr. to give 196 mg. of $KHCO_3$ (94% yield). The filtrate was evaporated *in vacuo* at room temperature, extracted with Et_2O, washed with H_2O, and dried over Na_2SO_4. Removal of the solvent left 394 mg. (97% yield) of a colorless viscous oil (IX), b.$p_{0.04}$ 135~137°. This oil was induced to crystallize on addition of petr. ether and recrystallized from petr. ether-Et_2O to colorless needles, m.p. 47~49°. *Anal.* Calcd. for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found : C, 73.90; H, 9.46. $[\alpha]_D^{20}$ +176.7°±2° (c=1.067, dioxane). UV λ_{max}^{EtOH} mμ : 237.5 (ε 9620). IR ν_{max}^{Nujol} cm^{-1} : 3445 (O-H), 1641 (C=O), 1603 (C=C), 996, 870.

Ozonolysis of (IX) and Hydrogen Peroxide Oxidation of the Ozonide——A solution of 950 mg. of (IX) in 15 cc. of AcOEt was treated with O_3 stream (3.2% O_3). at −75° After 2.0 equiv. of O_3 was absorbed, the solution was allowed to stand at −75° for 30 min. and the solvent was removed in high vacuum at room temperature, leaving a yellow oil. A mixture of this residue and 10 cc. of 30% H_2O_2 was stirred at room temperature for 3.5 hr., during which time $KHCO_3$ solution was added dropwise to this mixture in order to neutralize the liberated acid, with Bromothymol Blue as an indicator; the reaction medium should be neutral or slightly acid at all times. This reaction mixture was extracted with Et_2O, the aqueous layer was made negative to color-test with ZnI_2-starch paper by addition of $NaHSO_3$ solution in an ice bath, acidified to Congo Red with 2*N* H_2SO_4, salted out with Na_2SO_4, and extracted with Et_2O. The Et_2O extract was washed with H_2O, dried over Na_2SO_4, and evaporated giving 950 mg. of a colorless oil (XIa). Application of diazomethane to this oil afforded 730 mg. of its dimethyl ester (XIb), a mobile oil, which was distilled to yield 570 mg. of a colorless oil, b.$p_{1.5}$ 134°, n_D^{21} 1.4516, $[\alpha]_D^{24}$ +17.1° ± 2° (c=1.028, dioxane). *Anal.* Calcd. for $C_{13}H_{22}O_5$: C, 60.44; H, 8.59. Found : C, 60.65; H, 8.43. IR ν_{max}^{film} cm^{-1} : 1740 (C=O), 1713 (C=O), 1256, 1200, 1173.

Oxidation of (XIb) with Trifluoroperacetic Acid——A solution of CF_3COOOH was prepared by dropwise addition of a solution of 1.9 g. (4 equiv.) of $(CF_3CO)_2O$ in 2 cc. of CH_2Cl_2 to a suspension of 330 mg. (3.5 equiv.) of 80% H_2O_2[*6] in 1 cc. of CH_2Cl_2 with stirring in an ice bath. This solution was added dropwise to a stirred suspension of 3.3 g. of finely ground anhyd., Na_2HPO_4 in a solution of 570 mg. of (XIb) in 10 cc. of CH_2Cl_2 over a 15-min. period. During the addition, exothermic reaction was noted. The mixture was stirred for 5 hr., allowed to stand overnight at room temperature, and refluxed for 1 hr. The insoluble salt was collected on a filter and washed thoroughly with CH_2Cl_2. The combined filtrates was washed with $NaHSO_3$ solution, H_2O, $KHCO_3$ solution, and H_2O, dried over Na_2SO_4, and evaporated, giving 536 mg. of a colorless oil. Since it was indicated by the infrared spectrum and the elemental analysis that this oil still contained ca. 30% of the starting material (XIb), this oxidation procedure was repeated. The repeated oxidation product was purified as above, and a mobile oil was obtained, whose distillation gave 490 mg. of a colorless oil (XII), b.$p_{2.5}$ 139°, $[\alpha]_D^{21}$ +16.7°±2° (c=1.466, dioxane). *Anal.* Calcd. for $C_{13}H_{22}O_6$: C, 56.92; H, 8.08. Found : C, 57.46; H, 8.22. IR ν_{max}^{film} cm^{-1} : 1740 (C=O), 1257, 1197, 1172, 1134, 1077, 987.

Saponification of (XII)——A mixture of 5.0 g. of (XII) in 200 cc. of MeOH and 11 g. of K_2CO_3 in 10 cc. of H_2O was refluxed for 2 hr. on a steam bath. The residue obtained upon removal of the solvent was dissolved in a small amount of H_2O and extracted with Et_2O. The aqueous layer was acidified to Congo Red with conc. H_2SO_4, heated on a steam bath for 5 min., and extracted with Et_2O. The Et_2O extract was extracted with saturated $KHCO_3$ solution and the Et_2O layer was washed with saturated Na_2SO_4 solution, dried over Na_2SO_4, and Et_2O was evaporated giving 550 mg. of a pale yellow mobile oil (XIV). The above $KHCO_3$ extract was acidified with 4*N* H_2SO_4, salted out with Na_2SO_4, and extracted with Et_2O. This Et_2O extract was washed with saturated Na_2SO_4 solution, dried over Na_2SO_4, and evaporated giving a pale yellow oil, which was crystallized by seeding with synthetic (+)-2-methylglutaric acid; yield, 2.7 g. Recrystallization from benzene gave 950 mg. of colorless prisms (XIII), m.p. 85~86°, $[\alpha]_D^{13}$ +17.9°±1° (c=3.274, dioxane). *Anal.* Calcd. for $C_6H_{10}O_4$: C, 49.31; H, 6.90. Found : C, 49.59; H, 6.88.

[*6] 80% H_2O_2 was prepared by distillation of 30% H_2O_2 and *p*-cymene.

The mixed melting point of (XIII) with synthetic (+)-2-methylglutaric acid, m.p. 83~84°, was 83~85°, and that with synthetic (±)-2-methylglutaric acid, m.p. 80~82°, was 64~70° (see Table I).

Synthesis of (+)-2-Methylglutaric Acid——As shown in Chart 3, reduction of levulinic acid with a solution of $NaBH_4$ in 5% NaOH afforded (±)-4-hydroxyvaleric γ-lactone in 71% yield. A solution of this lactone in dehyd. EtOH was saturated with dehyd. HBr, and allowed to stand in a stoppered bottle at room temperature overnight. This operation gave ethyl (±)-4-bromovalerate in 76% yield, and refluxing with KCN in EtOH for 10 hr. led to ethyl (±)-4-cyanovalerate. Saponification of this cyanoester with KOH afforded (±)-2-methylglutaric acid, colorless prisms, m.p. 80~82° (from benzene). Resolution of this acid with strychinine by Berner's method8) gave (+)-2-methylglutaric acid, colorless prisms, m.p. 83~84°, $[\alpha]^{19}_{D}$ +15.4° ±2° (c=1.075, dioxane).

The authors are indebted to Mr. S. Inaba for optical rotatory data, to Dr. T. Kubota and Mr. Y. Matsui for infrared analyses, and to the members of Analysis Room of this Laboratory for elementary microanalyses.

Summary

Attempt was made for direct determination of the absolute configuration of methyl group at C-4 and C-10 in guaiol (I) by degradation of an α,β-unsaturated ketone (IX) derived from dihydroxyguaiol (II). Since S-(+)-2-methylglutaric acid (XIII) and 4-hydroxyvaleric γ-lactone (XIV) were obtained, the C-4 methyl group in guaiol possesses the α-configuration and guaiol should be represented by (XV).

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101. Hitoshi Minato : Studies on Sesquiterpenoids. II. Absolute Configuration of Guaiol. (2).[*1] Absolute Configuration of the Methyl Group at C-10 in Guaiol, and of Nepetalinic Acids and Iridolactones.

(*Research Laboratory, Shionogi & Co., Ltd.*[*2])

In the preceding paper,1),[*1] it was shown that the elucidation of the absolute configuration of guaiol was attempted and S-(+)-2-methylglutaric acid (V) and 4-hydroxyvaleric γ-lactone (VI) were obtained through (IIIa), (IIIb), and (IV) by degradation of an α,β-unsaturated ketone (II) (see Chart 1). These results led to the conclusion that the C-4 methyl group in guaiol possesses the α-configuration.[*3] In this paper will be reported the absolute configuration of the C-10 methyl group in guaiol. It was already discussed in Part I[*1] of this series that the C-10 methyl group in the ester (IV) (in Chart 1) kept its original configuration. This ester (IV), on saponification with potassium carbonate in methanol, gave S-(+)-2-methylglutaric acid (V) as well as 4-hyroxyvaleric γ-lactone (IV).

4-Hydroxyvaleric γ-lactone, b.p$_{23}$ 99~100°, thus obtained showed a negative optical rotation, $[\alpha]^{23}_{D}$ −35.1°, and its infrared spectrum (film) was identical with that of the synthetic (−)-4-hydroxyvaleric γ-lactone,2) b.p$_{22}$ 97~98°, $[\alpha]^{23}_{D}$ −17.2° (see Chart 2).

[*1] Prat I : This Bulletin, **9**, 619 (1961).

[*2] Fukushima-ku, Osaka (湊　均).

[*3] The terms "α" and "β" are used according to the steroidal convention.

1) K. Takeda, H. Minato : Tetrahedron Letters, No. 22, 33 (1960).

2) P.A. Levene, H.L. Haller : J. Biol. Chem., **69**, 165 (1926).